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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/207,188	12/08/1998	MILAN S. BLAKE	2016-4005US1	6452

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EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/207,188	BLAKE ET AL.	
	Examiner	**Art Unit**	
	S. Devi, Ph.D.	1645	

--The MAILING DATE of this communication appears on the cover she t with the correspondence address --

THE REPLY FILED 09 October 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *09 September 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): Double Patenting Rejection.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☒ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Attachment*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *None*.

   Claim(s) objected to: *None*.

   Claim(s) rejected: *80 and 82-93*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *See Attcahment*

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ATTACHMENT TO ADVISORY ACTION

Applicants' After-final Amendment

1) Acknowledgment is made of Applicants' after-final amendment filed 10/09/03 in response to the final Office Action mailed 04/07/03.

Status of Claims

2) Claims 73-79 and 81 have been canceled via the amendment filed 10/09/03.

Claim 84 has been amended via the amendment filed 10/09/03.

Claims 80 and 82-93 are pending and are under examination.

The Michon Declaration

3) Acknowledgment is made of Applicants' submission of the Michon Declaration filed 09/09/03 under 37 C.F.R 1.132. The Declaration has been considered.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Moot

6) The rejection of claim 81 made in paragraph 13 of the Office Action mailed 01/11/02 (paper no. 17) and maintained in paragraph 22 of the Office Action mailed 10/18/02 (paper no. 25) under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 26-33 of the U.S. Patent 5,866,135, is moot in light of Applicants' cancellation of the claim.

7) The rejection of claim 81 made in paragraph 15 of the Office Action mailed 01/11/02 (paper no. 17) and maintained in paragraph 21 of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

8) The rejection of claims 80 and 82-93 made in paragraph 13 of the Office Action mailed

01/11/02 (paper no. 17) and maintained in paragraph 22 of the Office Action mailed 10/18/02 (paper no. 25) under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 26-33 of the U.S. Patent 5,866,135, is withdrawn in light of Applicants' arguments. While the US patent 5,866,135 did have claims directed to a vaccine for providing protection against group A streptococcal infection comprising the group A streptococcal polysaccharide of the same structure as the one recited in the instant claims, conjugated to a protein, there were no claims directed to a method of using such a product in elicitation of protective antibodies in a mammal.

Rejection(s) Maintained

9) The rejection of claims 80 and 82-93 made in paragraph 15 of the Office Action mailed 01/11/02 (paper no. 17) and maintained in paragraph 21 of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is maintained for reasons set forth therein and here below.

Applicants point to Example 7 and Table IV and repeat some of the same arguments previously submitted. Applicants also point to pages 16-17 of the specification and state that the commonly known 'capping' phenomena is believed to be associated with GASP-liposome conjugates and an increase in antibody titers. Applicants have replaced the recitation 'bacterial assay' with 'bactericidal assay'. Applicants assert that the antibodies described in Example 1, may be shown to be protective through a series of four types of experiments: (i) bactericidal assays; (ii) relationship between anti-CHO titers and opsonophagocytosis by human sera; (iii) studies of phagocytosis by human sera; and (iv) absorption assays. Applicants assert that an absorption assay that removes GASP-specific antibodies in sera also indicates that GASP-specific antibodies are protective by causing the sera to lose opsonophagocytic ability. With this, Applicants conclude that GASP-specific antibodies are specific to the GAS polysaccharide component of the conjugate in the claimed methods of eliciting protective antibodies. Applicants further submit the Michon Declaration under 37 C.F.R 1.132. The Declaration submits and discusses the Sabharwal abstract on active immunization/ protection results obtained with a group A streptococcal polysaccharide-tetanus toxoid conjugate mixed with alum adjuvant.

Applicants' arguments have been carefully considered, but are non-persuasive. The 'capping'

phenomena believed to be associated with GASP-liposome conjugates is irrelevant to the instantly claimed method which does not use a GASP liposome conjugate. The insufficiency of the disclosure in Example 7 and Table IV of the instant specification in overcoming the current scope of enablement rejection has been addressed previously. It was re-emphasized that a patent application claiming a method of eliciting a 'protective' immune response in a subject by administration of a conjugate vaccine to a mammal has to necessarily show *in vivo* protective ability of the conjugate vaccine in a mammal, **or** *in vitro* assay results that correlate with *in vivo* protective efficacy of the conjugate vaccine. Contrary to Applicants' contention, Example 1 of the specification does not teach that antibodies to the polysaccharide of "formula I" wherein n is 3 to 50, are 'protective'. Example 1 shows that Group A streptococcal infection caused by live streptococci induced variable levels of bactericidal group A carbohydrate antibodies in humans infected with these bacteria. Example 1 shows that not all sera from group A streptococcus-infected patients contain a geometric mean group A streptococcal carbohydrate antibody titer of >200,000. Example 1 shows that live whole cell group A streptococci, upon infection in humans, induced a geometric mean bactericidal antibody titer of >200,000 in some infected patients. The specification on page 17, lines 22 and 23, recognizes that such whole cell streptococci are not desirable for use as a vaccine. The infection-induced antibodies in the human sera were induced by the native and non-depolymerized GASP presented to the host immune system on the surface of live whole cells of streptococci. The specification in the last paragraph of page 8 states that a CHO antibody titer of >200,000 (i.e., antibodies induced by group A streptococcal infection) represents 80% killing in the bactericidal assay. However, this bactericidal assay was performed with the sera of humans who were **not** immunized with the polysaccharide of formula I (wherein n=3 to 50) conjugated to a protein or a protein fragment. The immunogen recited in the instant claims is not live whole cell group A streptococcus, but a polysaccharide of formula I (wherein n is 3 to 50) conjugated to a protein or a protein fragment after modification or treatment of the polysaccharide with several chemicals. In order for formula I polysaccharide-protein conjugate, or formula I polysaccharide-protein fragment conjugate of the instant invention to be used in a method of eliciting a GASP-specific 'protective' immune response in a mammal, the conjugate (**not** the live whole cell Group A streptococci), with or without a clinically acceptable adjuvant, is **required** to induce 'protective' antibodies specific to

group A streptococcal polysaccharide, or a geometric mean level of ELISA GASP antibodies in a mammal immunized with the conjugate (as opposed to live whole cell Group A streptococci), which antibody level is correlative of 'protection'. As set forth in paragraph 21 of the Office Action mailed 01/11/02 (paper no. 17), Example 7 and Table IV show that rabbits immunized with the native unconjugated GASP elicited a geometric mean base line anti-GASP ELISA titer of $\leq$100 after the first, second and third immunizations. After first immunization, a saline solution of a GASP having an assumed molecular weight of about 10 Kd (i.e., n=about 20) and covalently coupled to tetanus toxoid protein induced the same base line titer of GASP antibodies (i.e., $\leq$100) in rabbits as that elicited by the uncoupled native GASP. This conjugate in saline elicited measurable GASP antibody titers by ELISA after the second and third immunizations. However, the geometric mean ELISA titer elicited by the conjugate was nowhere near 200,000. Even when rabbits were immunized with this GASP conjugate admixed with a clinically acceptable adjuvant, such as aluminum hydroxide or ST, the geometric mean ELISA titer elicited after three immunizations was nowhere near 200,000. Clearly, the claimed method of eliciting 'protective' antibodies specific to GASP in a mammal by administration of a formula I GASP-protein conjugate wherein n is about 20 (let alone a formula I GASP-protein fragment conjugate), with or without a clinically acceptable adjuvant, is not enabled. Rabbits immunized with the formula I GASP-protein conjugate admixed in clinically unacceptable adjuvants, such as CFA and IFA, elicited a geometric mean ELISA antibody titer that exceeded 200,000 following the second and third immunizations. However, it is important to note that CFA and IFA are not acceptable in the art of vaccines for use in a human or a human child. There is neither any showing, nor is it predictable that one skilled in the art can reproducibly and successfully practice the claimed method using a formula I polysaccharide-protein conjugate or a formula I polysaccharide-protein conjugate wherein n is 3 to 50. No opsonophagocytic or absorption assay results with the sera obtained by immunizing a mammal with the conjugate recited in the instant claims have been disclosed. Thus, Applicants' own specification provides *prima facie* evidence for a lack of scope of enablement for the claimed method.

The Sabharawal abstract provides data showing that active immunization of mice with a group A streptococcal polysaccharide of undisclosed structure and size (n), conjugated to tetanus toxoid, protected mice against infection with specific types of group A streptococci, when

administered along with an adjuvant, such as, alum. The Sabharwal group A streptococcal polysaccharide is not of the same formula, or of the same size as the one recited in the instant claims, wherein the structure of the polysaccharide has formula I and n number of 3 to 50. Moreover, the Sabharawal conjugate elicited protective immunity in mice only when administered in alum. The method of instant claims 80, 82-89, 92 and 93 use a polysaccharide of a specific formula and specific size conjugated to a protein or a protein fragment, in the absence of an adjuvant. Therefore, while the Sabhrawal abstract demonstrates the protective efficacy of a full length group A streptococcal polysaccharide of undisclosed formula and size conjugated to tetanus toxoid only when administered with alum, it does not enable a method of eliciting protective antibodies specific to group A streptococcal polysaccharide in a mammal, including a human or human child, by administration of a group A streptococcal polysaccharide of the specifically recited formula I, wherein n=3 to 50, which is conjugated to a protein or a protein fragment, with or without an adjuvant. Even with regard to the group A streptococcal polysaccharide of undisclosed structure and size, the Sabharwal data supports the observation described in Example 7 of the instant specification in that induction of polysaccharide-specific immunity requires administration of the conjugate along with an adjuvant. The disclosure of the Sabharwal abstract does not enable the instantly claimed method. The instant specification is enabling for a method of eliciting an immune response to group A streptococcal polysaccharide in a mammal comprising administering an effective amount of a group A streptococcal polysaccharide-tetanus toxoid conjugate, wherein the polysaccharide has the structure of formula I, n being 3 to 50, but is not enabled for a method of eliciting a 'protective' immune response, as claimed, in a mammal (including a rabbit, human or a human child) specific to group A streptococcal polysaccharide. The rejection stands.

Remarks

10) Claims 80 and 82-93 stand rejected.

11) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1 (CM1). The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax

number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

12) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

October, 2003

S. DEVI, PH.D.
PRIMARY EXAMINER